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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,356	07/24/2003	Michael R. Hale	VPI/00-122 DIV2 US	1551

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EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	**PAPER NUMBER**
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,356	HALE ET AL.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,18-23,27,28,30,33,35,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-13 and 18-23* is/are allowed.

6)☒ Claim(s) *27,28,30,33,35,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13, 18-23, 27, 28, 30, 33, 35, 37 and 39 are currently pending in the instant application. Claims 1-13 and 18-23 appear allowable and claims 27, 28, 30, 33, 35, 37 and 38 are rejected.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 January 2007 has been entered.

Response to Amendment and Arguments

Applicant's amendment and arguments filed 25 January 2007 have been fully considered and entered into the application. In regards to claim 23, applicants' amendment and arguments have been persuasive and the rejection of claim 23 is withdrawn. In regards to claims 27, 28, 30, 33, 35, 37 and 38, applicants' arguments have been considered but they are not persuasive.

Applicant argues that the specification along with Illenberger, Raghunandan, and Fukanaga clearly show that there is a reasonable correlation between the inhibitors of the invention, their ERK2 inhibitory activity and the use of these compounds to treat Alzheimer's disease. These arguments are not persuasive as Fukunaga is only speculative as Fukunaga only postulates that ERKS are attractive candidates to

mediate morphological differentiation and promote survival in neurons and only states that their inhibition may mediate physiological and pathological evens such as Alzheimer's disease. Illenberger is also only speculative and is concerned mostly with the phosphorylation at S214 by PKA or an equivalent kinase and that the phosphorylation of this residue strongly decreases the tau-microtubule interaction *in vitro.* There is no data provided in Illenberger regarding the in vivo treatment of Alzheimer's disease. While ERK2 was known at the time of the invention to mediate the phosphorylation of tau, see Raghunandan, the Raghunandan references is only speculative and does not provide any correlation to in vivo treatment as the conclusion is that it would be of great interest to determine which of these phosphorylation reactions would be important in vivo. Note Hoffman V. Klaus 9 USPQ2d 1657 regarding the standard of testing that is necessary to establish the likelihood of in vivo use. Also see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Any evidence relied on by applicants must clearly show a reasonable expectation of in vivo success. See MPEP 2164.05(a). The references provided and the specification do not show a reasonable correlation between the inhibitors of the invention, their ERK2 inhibitory activity and the use of these compounds to treat Alzheimer's as Fukunaga, Illenberger and Raghunandan do not discuss any compound, let alone a compound of similar structure to applicants' instantly claimed compounds. Receptor activity is generally

unpredictable and a highly structure specific area, and the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the compounds of the claims and to extrapolate to the in vivo treatment of Alzheimer's disease.

Applicant argues that the specification along with Chang clearly shows that there is a reasonable correlation between the inhibitors of the inventions, their ERK2 inhibitory activity and the use of these compounds to treat allergy/asthma. This argument is not found persuasive as the Chang reference does not disclose any compound of similar structure to applicants' claimed compounds. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided of is insufficient for one of ordinary skill in the art in order to extrapolate to the compounds of the claims and to extrapolate to the in vivo treatment of asthma. The Chang reference is speculative as it only proposes that a cAMP-dependent pathway may constituted an important component for regulating eosinophil survival/apoptosis and that cAMP may inhibit eosinophil apoptosis through the activation of PKA and of the subsequent MAPK in part. Additionally, the Chang reference, states that PD098059 is shown to selectively inhibit MAPK/ERK kinase activity. PD098059 is not structurally related to the instantly claimed compounds as PD098059 is 2'-amino-3-'methoxyflavone. Therefore, the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the compounds of the claims and to extrapolate to the in vivo treatment of asthma.

Applicant argues that the specification along with Slevin, Namura and Kodama, clearly show that there is a reasonable correlation between the inhibitors of the invention, their ERK2 inhibitory activity and the use of these compounds to treat the

cardiovascular diseases recited in the amended claims 27 and 35. This argument is not persuasive as the references provided do not disclose compounds of similar structure to the claimed invention. See Namura which is concerned with U0126, which differs materially in structure and composition from the claimed compounds as U0126 does not even include a pyrrole or oxazole ring. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided of is insufficient for one of ordinary skill in the art in order to extrapolate to the compounds of the claims and to extrapolate to the in vivo treatment of the claimed cardiovascular diseases. Kodama provided is drawn to in vitro activity, the uses covered by the claims are not enabled based solely on the assay testing. Various studies reported for compounds in clinical development rely on animal models and not simply assay testing as done herein. Note Hoffman V. Klaus 9 USPQ2d 1657 regarding the standard of testing that is necessary to establish the likelihood of in vivo use. Lastly, each of the references are speculative, see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. Kodama concludes that further studies are needed to clarify the precise role of the Raf-1/MEK/ERK pathway in g-130-mediated cardiac hypertrophy, page H1643. Namura is speculative in that the MEK inhibition may increase the resistance of tissue to ischemic injury, page 11569. Slevin is speculative in that phosphorylation of MAP kinase may be associated with increase in expression of VEFG and that these signal transduction evens could be important determinants of the extent of neuronal survival and/or angiogenic activity in

the recovering brain tissue. Therefore, the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the compounds of the claims and to extrapolate to the in vivo treatment of the claimed cardiovascular diseases.

Applicant argues that the specification along with Kortylewski, Hoshino, Frey, and Putz, clearly show that there is a reasonable correlation between the inhibitors of the invention, their ERK2 inhibitory activity and the use of these compounds to treat the cancers recited in the claims. This argument is not persuasive as the references provided do not disclose compounds of similar structure to the claimed invention. See wherein Kortylewski is concerned with PD098059. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided of is insufficient for one of ordinary skill in the art in order to extrapolate to the compounds of the claims and to extrapolate to the in vivo treatment of the claimed cancers. Hoshino, Kortylewski, Putz and Frey provided are drawn to in vitro activity, the uses covered by the claims are not enabled based solely on the assay testing. Various studies reported for compounds in clinical development rely on animal models and not simply assay testing as done herein. Note Hoffman V. Klaus 9 USPQ2d 1657 regarding the standard of testing that is necessary to establish the likelihood of in vivo use. Lastly, some of the references provided are speculative, see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. Hoshino is speculative in that specific inhibitors may be developed against signaling molecules such as MPA kinases and MEK for cancer therapy, page 820.

Kortylewski is speculative in that there is potential of novel therapeutic approaches targeting members of the Ras-Raf-MAPK pathway in the treatment of human melanoma. Frey is speculative in that the studies suggest that the Ras/MAPK pathway may be one of the important signaling pathways that mediate the growth inhibitory response to TGFb in untransformed epithelial cells, page 42. Therefore, the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the compounds of the claims and to extrapolate to the in vivo treatment of the claimed cancers.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 28, 30, 33, 35, 37 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention of claims 23 and 27-41 is the method of treatment of a disease selected from breast cancer, colon cancer, kidney carcinoma, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, stroke, restenosis, cardiomegaly, artherosclerosis, myocardial infarction, congestive heart failure, Alzheimer's Disease and asthma.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of the above listed diseases, whether or not the disease is effected by the inhibition of AKT and ERK would make a difference.

Applicants are claiming methods which include the treatment of various diseases such as stroke, certain cancers and Alzheimer's disease, etc.

Applicants' claims are therefore drawn to the treatment of Alzheimer's disease. It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease. (URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html.

Furthermore, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple

anatomic locations" (see page 2050). Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease" (pg. 1994).

In regards to asthma, chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells.

Stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, this trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Applicants claimed compounds useful in medical therapy also includes the treatment of cancers. The state of the prior art is that cancer therapy remains highly

unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al. page 531) Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art (Lala et al. page 91) that the role of NO in tumor biology remains incompletely understood with both the promotion and inhibition of NO mentioned for the treatment of tumor progression and only certain human cancers may be treated by selected NO-blocking drugs. These example shows that there are different cellular mechanisms, the unpredictability in the art and the different treatment protocols.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the inhibition of AKT and ERK one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role the inhibition of AKT and ERK and, for example, since it is known that there is no known cure for Alzheimer's disease and treatment protocols for Alzheimer's disease depend on the stage of the disease.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the listing of diseases applicant considers as treatable by the inhibition of ERK and AKT found on pages 50-53, 45 and 46. There are no working examples present for the treatment of any specific disease or disorder.

Test assays and procedure are provided in the specification at pages 58-63 for only AKT3 and ERK2. However, the disclosure does not provide how this in vitro data correlates to the treatment of the assorted list of disorders of the instant claims.

The uses covered by the claims are not enabled based solely on the assay testing reported in the specification. Various studies reported for compounds in clinical development rely on animal models and not simply assay testing as done herein. Note Hoffman V. Klaus 9 USPQ2d 1657 regarding the standard of testing that is necessary to establish the likelihood of in vivo use. Also see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Any evidence relied on by applicants must clearly show a reasonable expectation of in vivo success for any additional diseases that may still be embraced in response to this action. See MPEP 2164.05(a).

Further, there is no disclosure regarding how all types of the diseases having divers mechanisms are treated. Receptor activity is generally unpredictable and a

highly structure specific area, and the data provided of is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is the treatment of a disease selected from breast cancer, colon cancer, kidney carcinoma, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, stroke, restenosis, cardiomegaly, artherosclerosis, myocardial infarction, congestive heart failure, Alzheimer's Disease and asthma.

The disorders encompassed by the instant claims include, for example, Alzheimer's disease and stroke, etc. some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all diseases would be benefited (treated) by the inhibition of AKT or ERK and would furthermore then have to determine which of the claimed compounds would provide treatment of which disease, if any.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment of a disease selected from breast cancer, colon cancer, kidney carcinoma, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, stroke, restenosis, cardiomegaly, artherosclerosis, myocardial infarction, congestive heart failure, Alzheimer's Disease and asthma as a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the instant claims in order to practice the claimed invention. (Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the

instantly claimed methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by deleting the method claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

14 March 2007

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